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published in
Stroke
1999

DOI (link to publisher)
10.1161/01.STR.30.7.1312

document version
Publisher's PDF, also known as Version of record

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Stroke 1999, 30:1312-1318
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

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Background and Purpose—Most population-based studies indicate that a considerable proportion of hypertensive subjects are undertreated and that undertreatment is more prevalent among hypertensive men than among hypertensive women. The aim of our study was to investigate the consequences of undertreatment of hypertension for women and men in terms of stroke occurrence.

Methods—Approximately 45 000 men and women aged ≥20 years were examined in 2 population-based studies in the Netherlands. A cohort of 2616 hypertensive subjects (pharmacologically treated hypertensives and untreated hypertensives who needed pharmacological treatment according to the severity of their hypertension and the coexistence of additional cardiovascular risk factors) was selected for a follow-up study. Follow-up (mean duration, 4.6 years) was complete for 2369 (91%) of the enrolled hypertensive subjects.

Results—Compared with treated and controlled hypertensives, the relative risks of stroke for treated and uncontrolled hypertensives and for untreated hypertensives who needed treatment were 1.30 (95% CI, 0.70 to 2.44) and 1.76 (95% CI, 1.05 to 2.94), respectively. These relative risks and the prevalence of (undertreated) hypertension in the total population of 45 000 subjects were used to estimate the number of strokes in the Netherlands attributable to undertreatment. Among hypertensive men and women aged ≥20 years in the Netherlands, the proportions of strokes attributable to treated but uncontrolled blood pressure were 3.1% (95% CI, −5.2% to 18.7%) and 4.1% (95% CI, −7.2% to 20.7%), respectively. For untreated hypertensive men and women who should have been treated, these proportions were 22.8% (95% CI, 0.8% to 38.4%) and 25.4% (95% CI, 0.5% to 42.5%), respectively.

Conclusions—Increasing the detection of hypertension and improving adherence to current guidelines might prevent a considerable proportion of the incident strokes among hypertensives. The potential impact of achieving control of blood pressure in patients already being treated on the reduction of strokes requires further investigation. **(*Stroke*. 1999;30:1312-1318.)**

Key Words: hypertension ■ population-based studies ■ stroke ■ treatment

Hypertension is one of the most important risk factors for cardiovascular diseases in general and for cerebrovascular diseases in particular.[1] Although the beneficial effect of pharmacological treatment of hypertension on the incidence of coronary heart diseases and cerebrovascular diseases has been demonstrated in several controlled clinical trials,[2] most population-based studies indicate that a large proportion of treated hypertensive patients still have elevated blood pressure,[3] and a considerable proportion of hypertensive patients are not treated with antihypertensive drugs.[4] However, not all hypertensives need pharmacological treatment because, according to several guidelines on the management of hypertension, this depends on the severity of hypertension and in moderate hypertension may depend on the coexistence of additional cardiovascular risk factors.[5–7] In a population-based study among men and women aged 20 to 59 years in the Netherlands, we demonstrated that approximately 42% and 29% of the pharmacologically treated men and women, respectively, still had elevated blood pressure levels. Of those hypertensive men and women not treated pharmacologically, 53% and 34%, respectively, should have been treated when additional cardiovascular risk factors and the severity of hypertension were taken into account.[8]

The consequences of undertreatment of hypertension in terms of cardiovascular disease occurrence have been studied in observational studies. However, these studies had several limitations. First, most studies were restricted to either uncontrolled blood pressure among treated hypertensives[9–12]

Received February 22, 1999; final revision received April 15, 1999; accepted April 16, 1999.

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or to untreated hypertension.[13–19] Second, in none of the studies was the coexistence of additional cardiovascular disease risk factors taken into account to assess the need for pharmacological treatment. Finally, in most of these studies, treated hypertensives were compared with the remainder of the population or normotensive controls[9,13–20] or with untreated hypertensives irrespective of their need for treatment.[13,14] Thus, the reference groups in these studies were not comparable with the treated hypertensives with respect to risk of cardiovascular disease, and this may have led to confounding by the indication for the treatment of hypertension.[21]

The aim of our study was to estimate the proportion of incident strokes attributable to undertreatment of hypertension in men and women, taking into account the shortcomings of previous studies.

Subjects and Methods

Data

For the present study we used data from 2 population-based studies in the Netherlands. The first study, the Monitoring Project on Cardiovascular Risk Factors, was started in 1987 as a cross-sectional study in Amsterdam, Maastricht, and Doetinchem. In Doetinchem this study was continued as a prospective follow-up study by reexamining the subjects examined in 1987 again in 1993. The second study, the Rotterdam Study, was started in 1990 in Rotterdam as a population-based prospective follow-up study.

The Monitoring Project on Cardiovascular Risk Factors

This study was conducted from 1987 to 1991. Each year a new random sample of men and women aged 20 to 59 years in Amsterdam, Maastricht, and Doetinchem was selected. The design of this study has been described in detail elsewhere.[22] The overall response rate in Amsterdam, Maastricht, and Doetinchem was 45%, 58%, and 62%, respectively. Several characteristics such as educational level, smoking, alcohol use, height, and weight of nonrespondents and respondents have been evaluated in previous studies.[8] The results of these studies suggested that no substantial selection had taken place with respect to these characteristics.

The Rotterdam Study

This study on the occurrence and determinants of chronic disabling diseases at older ages was started in 1990. All 10 275 residents of a suburb of Rotterdam aged ≥55 years were invited to participate; 7983 (78%) subjects agreed to participate. The design of this study has been described in detail elsewhere.[23] The baseline measurements took place until 1993.

Baseline Measurements

Information on demographic variables, current health status, medical history, family history of diseases, smoking habits, and current use of medication was obtained during a home interview in the Rotterdam study, whereas self-administered questionnaires were used in the Monitoring Project on Cardiovascular Risk Factors. The self-administered questionnaires were checked at the study center with the participant for completeness. In both studies the physical examinations were performed by either trained technicians or physicians according to a standardized protocol. Blood pressure, weight, and height were measured, and blood was drawn for total cholesterol and HDL cholesterol determination. A random zero sphygmomanometer was used to measure blood pressure twice with the subject in sitting position. Systolic blood pressure (SBP) was recorded at the appearance of sounds (first-phase Korotkoff), and diastolic blood pressure (DBP) was recorded at the disappearance of sounds (fifth-phase Korotkoff). For the analyses, we used the mean of 2 blood pressure measurements.

Follow-Up

For this study, we selected subjects who were treated pharmacologically for hypertension and subjects who were untreated but in need of pharmacological treatment for hypertension (see Definitions) at the baseline measurement in Rotterdam (1990–1993) and Doetinchem (1987–1991). The follow-up period in both studies started at the baseline examination and lasted until April 1, 1996, in Rotterdam, and until January 1, 1996, in Doetinchem. Information on fatal and nonfatal strokes was obtained through patient records of general practitioners (GPs) and the GPs' archives of specialists' reports.

Definitions

Hypertension was defined as DBP ≥95 mm Hg and/or SBP ≥160 mm Hg and/or use of antihypertensive drugs for hypertension. Subjects who said that they used blood pressure–lowering drugs and mentioned at least 1 drug with an approved indication for the treatment of hypertension were considered pharmacologically treated for hypertension. With regard to cardiovascular drug use, it was previously demonstrated that concordance between medication use according to patient interview and pharmacy records is very high.[24,25] Three categories of hypertensives were distinguished according to the Dutch guidelines for the management of hypertension.[5] First, the reference group was defined as pharmacologically treated hypertensives whose blood pressure was below the treatment goal of the Dutch guidelines (DBP ≤90 mm Hg and SBP ≤160 mm Hg). The second group included pharmacologically treated hypertensives whose blood pressure was above this treatment goal (DBP >90 mm Hg or SBP >160 mm Hg). The third group consisted of untreated hypertensives who need pharmacological treatment when the coexistence of additional cardiovascular risk factors was taken into account. According to the Dutch guidelines, hypertension should be treated pharmacologically when the DBP is between 100 and 105 mm Hg and 1 or more cardiovascular risk factors are present, or when the SBP is between 160 and 180 mm Hg and 1 or more cardiovascular risk factors are present, or when DBP or SBP are >105 mm Hg or >180 mm Hg, respectively. The following additional cardiovascular risk factors should be evaluated according to these guidelines: sex (male), current smoking, hypercholesterolemia (total cholesterol ≥6.5 mmol/L), diabetes, target organ disease, age ≥60 years, and cardiovascular disease among parents or sisters or brothers aged <60 years.

Strokes that could be confirmed by specialists' letters to the GPs and strokes that were certain according to the GP were included for the analysis, whereas events that were probable according to the GP were excluded. The end point of interest was a first or recurrent fatal or nonfatal stroke (*International Classification of Diseases, Tenth Revision* codes I60 to I69), excluding transient ischemic attacks (TIA) during follow-up.

History of cardiovascular disease was defined as a self-reported history of any cardiovascular disease or written information from the GPs that indicated presence of any cardiovascular disease, excluding cerebrovascular diseases. History of cerebrovascular disease was defined as a self-reported history of stroke or TIA, confirmed by written information from the GPs.

Analyses

Estimation of Risk of Stroke Attributed to Undertreatment of Hypertension

To study the association between undertreatment and incidence of stroke, the Cox proportional hazards model was used, and multivariately adjusted relative risks (RRs) and their 95% CIs[26] were calculated. Analyses were initially performed separately for the Doetinchem study and the Rotterdam study to evaluate effect-modification due to differences in study design. The RRs of undertreatment of hypertension for the occurrence of stroke were virtually the same in the Doetinchem study and the Rotterdam study. Therefore, the results from the combined analysis are presented.

In addition to the evaluation of all subjects simultaneously, subgroup analyses were performed after exclusion of patients without a history of cerebrovascular disease and after exclusion of

TABLE 1. Baseline Characteristics of Men and Women Aged ≥20 Years by Classification of Undertreatment of Hypertension

	Treated, Controlled*	Treated, Uncontrolled†	Untreated but Should Be Treated
No. of subjects	879	482	1008
Women	593 (67.5%)	312 (64.7%)	538 (53.4%)
Age (SD), y	65.8 (10.7)	65.3 (13.0)	66.6 (14.3)
Diabetes	59 (6.7%)	42 (8.7%)	75 (7.4%)
Smoking			
Never	360 (42.3%)	216 (45.5%)	395 (40.2%)
Current	170 (20.1%)	104 (21.9%)	233 (23.7%)
Former	318 (37.5%)	155 (32.6%)	354 (36.1%)
Total cholesterol, mmol/L	6.6 (1.2)	6.5 (1.2)	6.6 (1.3)
History of cardiovascular diseases‡	218 (24.8%)	103 (21.4%)	171 (17.0%)
History of TIA	39 (4.6%)	21 (4.4%)	28 (2.9%)
History of stroke	30 (3.4%)	23 (4.8%)	27 (2.7%)
Body mass index, kg/m^2	27.7 (4.0)	28.1 (4.3)	26.8 (3.8)
DBP, mm Hg	75.6 (8.8)	89.2 (11.9)	88.5 (13.6)
SBP, mm Hg	135.5 (14.3)	164.1 (19.7)	169.0 (14.9)
Mean duration of follow-up, y	4.8 (1.7)	4.7 (1.8)	4.3 (1.6)

*Controlled blood pressure, DBP ≤90 mm Hg and SBP ≤160 mm Hg.
†Uncontrolled blood pressure, DBP >90 mm Hg or SBP >160 mm Hg.
‡Excluding TIA and strokes.

patients with any history of cardiovascular disease. Furthermore, men and women and subjects aged <80 and ≥80 years (the efficacy of antihypertensive treatment at ≥80 years is unknown[2]) were analyzed separately.

All RR estimates were adjusted for age, history of diabetes, total cholesterol, body mass index, smoking, and history of cardiovascular disease. When men and women were analyzed together, adjustments were also made for sex, and in the analysis of all subjects irrespective of a history of cerebrovascular disease, adjustments were also made for a history of stroke or TIA. For the adjustment of RRs, smoking was categorized into never, former, or current smoking.

Estimation of Prevalences of Undertreatment of Hypertension

Age- and sex-specific prevalences of hypertension, treated and controlled hypertension, treated but uncontrolled hypertension, and untreated hypertension that should be treated were estimated among all subjects who were examined in all 4 cities in both population studies. These prevalence estimates were used to compute the number of subjects within these categories of hypertensives in the whole Dutch population.

Estimation of the Number of Incident Strokes Attributable to Undertreatment of Hypertension

Age- and sex-specific incidence rates of stroke among all hypertensives, treated and controlled hypertensives, treated but uncontrolled hypertensives, and untreated hypertensives who should be treated were computed (PYRS version 1.2) to estimate the number of incident strokes in these categories of hypertensives in the Netherlands in 1994. This was done by multiplying the age- and sex-specific estimated numbers of subjects within the different categories of hypertensives in the Netherlands in 1994 by the corresponding age- and sex-specific incidence rates. Subsequently, we estimated the proportions of incident strokes attributable to treated but uncontrolled blood pressure and untreated hypertension that should be treated within each of these categories of undertreatment as the ratio (RR−1)/RR. The adjusted RRs of exposed persons (treated but uncontrolled hypertensives or untreated hypertensives who should be treated) compared with unexposed persons (treated and controlled hypertensives) were used for the RR. These proportions were used to estimate the absolute number of incident strokes attributable to both types of undertreatment. Finally, these attributable numbers of incident strokes were expressed as percentages of the total number of incident strokes among all hypertensive subjects. We estimated 95% CIs of the attributable number of incident strokes according to the method of Rothman and Greenland.[27]

Results

Study Population

A total of 44 571 subjects (12 448 in Doetinchem, 11 488 in Amsterdam, 12 652 in Maastricht, and 7983 in Rotterdam) were examined in both population studies. After exclusion of pregnant women (n=306) and subjects with missing data (n=1665), 42 600 subjects remained available for the estimation of prevalences of hypertension and undertreatment of hypertension.

Hypertension was prevalent among 2072 subjects (28.9%) of the Rotterdam study and among 1096 subjects (9.4%) in Doetinchem. Subjects who did not need antihypertensive drug treatment according to the guidelines (n=552) were excluded from the analysis. Therefore, our study population comprised 2616 subjects pharmacologically treated for hypertension or untreated for hypertension but in need of pharmacological treatment. Follow-up was complete for 2369 subjects (90.6%).

The differences in baseline characteristics between those lost to follow-up and those for whom follow-up was complete were negligible (data not shown).

The number of hypertensives who were treated pharmacologically and had DBP <90 mm Hg and SBP <160 mm Hg was 879, whereas 482 subjects were treated pharmacologically but had DBP >90 mm Hg or SBP >160 mm Hg, and 1008 subjects were inappropriately not treated pharmacolog-

TABLE 2. Stroke Incidence Rates (per 1000 Person-Years) Among Hypertensive Subjects Aged ≥20 Years and RR Estimates by Classification of Undertreatment of Hypertension

	No. of Subjects	No. of Events	Rate*	RR (95% CI)†	RR (95% CI)‡
All subjects					
Treated, controlled	879	28	6.7	1.00	1.00
Treated, uncontrolled	482	19	8.2	1.24 (0.69–2.22)	1.30 (0.70–2.44)
Untreated, should be treated	1008	61	14.0	2.06 (1.31–3.22)	1.76 (1.05–2.94)
Men					
Treated, controlled	286	11	8.4	1.00	1.00
Treated, uncontrolled	170	6	7.3	0.87 (0.32–2.36)	1.29 (0.44–3.76)
Untreated, should be treated	470	23	10.6	1.26 (0.61–2.58)	1.81 (0.77–4.21)
Women					
Treated, controlled	593	17	5.9	1.00	1.00
Treated, uncontrolled	312	13	8.7	1.51 (0.73–3.10)	1.31 (0.60–2.87)
Untreated, should be treated	538	38	17.3	2.91 (1.64–5.17)	1.76 (0.90–3.44)

*Per 1000 person-years.
†Unadjusted RR.
‡All RRs are adjusted for age, smoking, total cholesterol, body mass index, history of cardiovascular diseases, and history of stroke or TIA. RRs for all subjects are also adjusted for sex.

ically for hypertension. Baseline characteristics of all 2369 hypertensive men and women stratified by these 3 categories are listed in Table 1. Most risk factors were evenly distributed across these categories. One important difference was a higher prevalence of past cardiovascular disease (excluding cerebrovascular disease) among pharmacologically treated hypertensives compared with untreated hypertensives who should have been treated. This difference was more pronounced for men than for women (data not shown). Prevalence of past cerebrovascular disease was also slightly higher for pharmacologically treated hypertensives.

Undertreatment of Hypertension and Risk of Stroke

During the follow-up period (mean duration, 4.6 years), 40 men and 68 women experienced a first or recurrent stroke. The number of fatal stroke events was 2 for men and 15 for women.

The crude incidence rates of stroke among treated hypertensives with controlled blood pressure levels, treated hypertensives with uncontrolled blood pressure levels, and untreated hypertensives who should have been treated were 6.7, 8.2, and 14.0 per 1000 person-years, respectively (Table 2).

Compared with treated hypertensives who had controlled blood pressure and after adjustment for potential confounding factors, treated hypertensives who had uncontrolled blood pressure levels had a 1.30-fold increased risk of stroke (not statistically significant), whereas untreated hypertensives who should have been treated had a 1.76-fold increased risk of stroke (Table 2). These RRs were similar for men and women. Exclusion of subjects with a history of cerebrovascular disease resulted in slightly increased RRs of treated but uncontrolled blood pressure and untreated hypertension that should be treated compared with treated and controlled blood pressure (1.47 [95% CI, 0.73 to 2.95] and 1.86 [95% CI, 1.04 to 3.33], respectively).

Additional analyses of subjects without any history of cardiovascular disease resulted in even higher RRs of treated but uncontrolled blood pressure and untreated hypertension that should be treated compared with treated and controlled blood pressure (2.0 [95% CI, 0.8 to 4.6] and 2.3 [95% CI, 1.1 to 4.8], respectively).

For subjects aged <80 years, the adjusted RRs of stroke of treated but uncontrolled blood pressure and untreated hypertension that should be treated were 1.4 (95% CI, 0.7 to 2.8) and 1.7 (95% CI, 0.9 to 3.0), respectively. For subjects aged ≥80 years, these RRs were 1.2 (95% CI, 0.2 to 5.6) and 2.6 (95% CI, 0.8 to 9.2), respectively. However, because of the small numbers we could not further investigate these associations by age.

Number of Incident Strokes Attributable to Undertreatment of Hypertension

The incidence rates of stroke after stratification for age, sex, and categories of hypertension (treated and controlled, treated but uncontrolled, untreated but should be treated) as derived from the 2 population studies are presented in Table 3. In both sexes the incidence rates increased with age. Furthermore, rates were highest in the untreated hypertensives who should be treated. The respective age-adjusted prevalences of hypertension (per 100 population), treated and controlled hypertension (per 100 hypertensives), treated but uncontrolled hypertension (per 100 hypertensives), and untreated hypertension that should be treated (per 100 hypertensives) were 11.2, 28.2, 15.5, and 39.7 for men, whereas for women these prevalences were 12.9, 39.4, 18.8, and 32.1. Age- and sex-specific prevalences were used to calculate the number of subjects in each of the categories of hypertension for the whole Dutch population in 1994 (data not shown). These numbers were subsequently multiplied by the corresponding incidence rates to estimate the absolute number of strokes in these categories of hypertensive (Table 3). The number of

TABLE 3. Incidence Rates (per 1000 Person-Years) and Number of Incident Strokes Among Hypertensives in the Netherlands in 1994*

	Hypertension		Treated and Controlled		Treated but Uncontrolled		Untreated but Should Be Treated	
Age, y	Rate	No.	Rate	No.	Rate	No.	Rate	No.
Men								
20–29	0.0	0	...	...	0.0	0	0.0	0
30–39	0.0	0	0.0	0	0.0	0	0.0	0
40–49	1.1	136	0.0	0	0.0	0	0.0	0
50–59	4.6	706	3.5	173	4.7	141	5.0	225
60–69	8.8	1274	7.6	409	11.5	255	10.0	637
70–79	15.7	1678	10.1	308	11.7	236	18.4	982
≥80	29.9	962	26.5	266	0.0	0	38.4	674
>20†	7.5	4757	6.5	1156	6.4	631	10.0	2518
Women								
20–29	0.0	0	0.0	0	0.0	0	0.0	0
30–39	0.0	0	0.0	0	0.0	0	0.0	0
40–49	0.0	0	0.0	0	0.0	0	0.0	0
50–59	3.2	463	0.0	0	5.6	170	3.5	88
60–69	3.8	730	2.9	272	3.1	92	3.8	245
70–79	10.6	2061	10.6	796	10.2	422	12.9	963
≥80	31.2	3460	15.3	398	22.0	489	43.4	2661
≥20†	8.8	6715	4.9	1466	8.2	1172	16.2	3957
Total								
≥20†	8.2	11 472	5.5	2622	7.5	1804	13.0	6475

Ellipses indicate no person-years in this stratum.

*Incidence rates (per 1000 person-years) were estimated from both population studies. Numbers of strokes were computed by multiplying the total number of subjects within each age- and sex-specific category of hypertension with the corresponding incidence rate.

†Weighted for the age distribution of the Dutch population in 1994.

strokes in women was more than twice the number of strokes in men.

The age-adjusted proportions of strokes among hypertensive men and women attributable to treated but uncontrolled blood pressure were 3.1% (95% CI, −5.2% to 18.7%) and 4.1% (95% CI, −7.2% to 20.7%), respectively (Table 4). For untreated hypertensive men and women who should have been treated, these proportions were 22.8% (95% CI, 0.8 to 38.4%) and 25.4% (95% CI, 0.5 to 42.5%), respectively. Among hypertensive subjects aged ≥20 years in the Netherlands in 1994, ≈26% (1230) of all incident strokes among hypertensive men and 29% (1975) of all incident strokes among hypertensive women were attributable to undertreatment of hypertension.

Discussion

In a previous study we showed that during the last decade in the Netherlands, a considerable proportion of hypertensive men and women aged 20 to 59 years were undertreated for hypertension.[8] In the present study we investigated the consequences of undertreatment of hypertension among men and women aged ≥20 years with respect to the occurrence of stroke. We demonstrated that untreated hypertensives who needed treatment according to the severity of their hypertension and the presence of additional cardiovascular risk factors had an increased risk of stroke compared with pharmacologically treated hypertensives whose blood pressure level was controlled. Among hypertensive men and women aged ≥20 years in the Netherlands, ≈1083 and ≈1702 incident strokes per year, respectively (23% and 25% of all incident strokes among hypertensive men and women, respectively) might be due to untreated hypertension that should have been treated. According to an average of several general practice registrations in the Netherlands,[28] ≈13 026 and ≈15 119 incident strokes occurred among men and women, respectively, in the whole Dutch population aged ≥20 years in 1994. On the basis of these figures, ≈8.3% and ≈11.3% of all incident strokes among men and women aged ≥20 years in the Netherlands were attributable to untreated hypertension that should have been treated. This is probably an underestimation since the definition of stroke was more strict in our study than in these general practice registrations. Because of the imprecise RR estimate of treated but uncontrolled blood pressure, we could not reliably estimate the number of strokes attributable to this type of undertreatment. However, the attributable fraction due to treated but uncontrolled blood pressure appears to be much lower than that due to untreated hypertension that should be treated.

Estimations of the proportion of a disease attributable to exposure are only valid when risk estimates and prevalence

TABLE 4. Number of Strokes Attributable to Undertreatment of Hypertension Among Hypertensives in the Netherlands in 1994

Age, y	Treated But Uncontrolled	Untreated but Should Be Treated	Total Undertreated
Men*			
20–29	...	...	...
30–39	...	...	...
40–49	...	...	...
50–59	33 (4.6)	97 (13.7)	129 (18.3)
60–69	59 (4.7)	274 (21.5)	333 (26.2)
70–79	55 (3.3)	423 (25.2)	478 (28.5)
≥80	...	290 (30.1)	290 (30.1)
≥20†	147 (3.1)	1083 (22.8)	1230 (25.9)
Women*			
20–29	...	...	...
30–39	...	...	...
40–49	...	...	...
50–59	39 (8.5)	38 (8.2)	77 (16.7)
60–69	21 (2.9)	105 (14.4)	127 (17.3)
70–79	98 (4.8)	413 (20.1)	512 (24.9)
≥80	114 (3.3)	1145 (33.1)	1259 (36.4)
≥20†	273 (4.1)	1702 (25.4)	1975 (29.4)
Total*			
≥20†	421 (3.7)	2785 (24.3)	3205 (27.9)

Values are number (percent) (percentage of all incident strokes among hypertensives). Ellipses indicate that no incident strokes were observed in these age strata.

*Attributable fractions (AF=[RR−1]/RR) of incident strokes were estimated for treated but uncontrolled hypertensive men, women, and all subjects together (adjusted RR of 1.30 was used) and for untreated hypertensive men, women, and all subjects together who should be treated (adjusted RR of 1.76 was used). The number of attributable incident strokes was calculated by multiplying the AFs of both types of undertreatment with the total number of incident strokes within both types of undertreatment.

†Weighted for the age distribution of the Dutch population in 1994.

estimates on which these attributable proportions are based are unbiased. Therefore, it is important to discuss several limitations of our study that could potentially have biased our estimated proportion of strokes attributable to undertreatment of hypertension.

First, blood pressure was measured only twice on 1 occasion. Because of within-person variability in blood pressure, the group of untreated hypertensives who should be treated will also comprise normotensive subjects.[8,29] Misclassification of normotensives as hypertensive has probably caused an underestimation of our RR estimates.

A second limitation of this study could be that the results in part may be caused by confounding by the indication for the treatment of hypertension. However, we compared a high-risk group of untreated hypertensives with additional cardiovascular risk factors with treated and controlled hypertensives, and the differences between untreated hypertensives who should be treated and treated hypertensives were only marginal with respect to the traditional cardiovascular risk factors at baseline. Furthermore, all RR estimates were adjusted for the potential confounding influence of other cardiovascular disease risk factors.

Third, it cannot be excluded that treated hypertensives with controlled blood pressure had lower pretreatment blood pressure levels than treated but uncontrolled hypertensives. We could not adjust for this in the analysis. Nonetheless, the excess risk of treated but uncontrolled blood pressure compared with treated and controlled blood pressure suggests that lowering blood pressure in hypertensives with uncontrolled blood pressure would reduce the risk of stroke among these hypertensive patients.

Fourth, we measured the status of undertreatment only at baseline, whereas during the follow-up period treatment could have been started in untreated hypertensives and control of blood pressure could have been achieved among treated hypertensives who were uncontrolled at the baseline measurements. Assuming that it is more likely that untreated hypertensives are going to be treated during follow-up than that treatment is stopped in treated hypertensives, the RR of untreated hypertension that should be treated was probably underestimated.

Finally, because of the small numbers, some reservation with regard to the precision of the estimated number of attributable strokes must be taken into account. The RR of treated but uncontrolled blood pressure and the number of strokes attributable to this type of undertreatment were not statistically significant. However, several other studies also found an increased risk of stroke among treated hypertensives with uncontrolled blood pressure compared with those with controlled blood pressure.[9,10,12,20] Furthermore, the increased risk of treated but uncontrolled blood pressure was consistent across the subgroups that we studied. Nonetheless, the number of strokes attributable to treated but uncontrolled blood pressure should be interpreted with caution.

Although the prevalence of undertreatment of hypertension was higher for hypertensive men than for hypertensive women, the proportion of incident strokes due to undertreatment was slightly smaller for men than for women. The absolute number of incident strokes attributable to undertreatment was also higher for hypertensive women than it was for hypertensive men. This can probably be explained by the higher number of elderly women, in particular at ages >70 years. Above this age the incidence rate of stroke was very high. Another explanation could be that the mortality from coronary heart disease is much higher among men than among women.[30–32] This could have resulted in a selective depletion of the pool of men who are at high risk for stroke, resulting in more women than men at high risk for experiencing a stroke event.[33]

This study provides one of the first estimates of the risk of stroke in the population in relation to the quality of treatment of hypertension. Our findings suggest that improvement of the detection of hypertension and adherence to the current guidelines on the management of hypertension might prevent a considerable proportion of incident strokes among hypertensive men and women. The potential impact of achieving control of blood pressure among those already treated on the reduction of stroke incidence remains uncertain.

Acknowledgment

This study was supported by a grant from the Stichting Maatschappelijke Aandachtsgebieden of the University of Utrecht.

References

1. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease, part 1: prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990;335:765–774.
2. Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull*. 1994;50:272–298.
3. Marques-Vidal P, Tuomilehto J. Hypertension awareness, treatment and control in the community: is the "rule of halves" still valid? *J Hum Hypertens*. 1997;11:213–220.
4. Klungel OH, de Boer A, Paes AH, Seidell JC, Bakker A. Sex differences in the pharmacological treatment of hypertension: a review of population-based studies. *J Hypertens*. 1997;15:591–600.
5. Walma EP, Grundmeijer HGLM, Thomas S, Prins A, van den Hoogen JPH, van der Laan JR. NHG-Standaard hypertensie (eerste herziening) [in Dutch]. *Huisarts Wet*. 1997;40:598–617.
6. Zanchetti A, Chalmers JP, Arakawa K, Gyarfas I, Hamet P, Hansson L, Julius S, MacMahon S, Mancia G, Menard J. The 1993 guidelines for the management of mild hypertension: memorandum from a WHO/ISH meeting. *Blood Press*. 1993;2:86–100.
7. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. Washington, DC: National Institutes of Health; 1997.
8. Klungel OH, de Boer A, Paes AH, Seidell JC, Nagelkerke NJ, Bakker A. Undertreatment of hypertension in a population-based study in the Netherlands. *J Hypertens*. 1998;16:1371–1378.
9. Trafford JA, Horn CR, O'Neal H, McGonigle R, Halford-Maw L, Evans R. Five year follow-up of effects of treatment of mild and moderate hypertension. *BMJ (Clin Res Ed)*. 1981;282:1111–1113.
10. Bulpitt CJ, Palmer AJ, Fletcher AE, Beevers DG, Coles EC, Ledingham JG, O'Riordan PW, Petrie JC, Rajagopalan BE, Webster J. Optimal blood pressure control in treated hypertensive patients: report from the Department of Health Hypertension Care Computing Project (DHCCP). *Circulation*. 1994;90:225–233.
11. Lindblad U, Rastam L, Ryden L, Ranstam J, Isacsson SO, Berglund G. Control of blood pressure and risk of first acute myocardial infarction: Skaraborg hypertension project. *BMJ*. 1994;308:681–686.
12. Alter M, Friday G, Lai SM, O'Connell J, Sobel E. Hypertension and risk of stroke recurrence. *Stroke*. 1994;25:1605–1610.
13. Thurmer HL, Lund-Larsen PG, Tverdal A. Is blood pressure treatment as effective in a population setting as in controlled trials? results from a prospective study. *J Hypertens*. 1994;12:481–490.
14. Yano K, McGee D, Reed DM. The impact of elevated blood pressure upon 10-year mortality among Japanese men in Hawaii: the Honolulu Heart Program. *J Chronic Dis*. 1983;36:569–579.
15. Clausen J, Jensen G. Blood pressure and mortality: an epidemiological survey with 10 year follow-up. *J Hum Hypertens*. 1992;6:53–59.
16. Merlo J, Ranstam J, Liedholm H, Hedblad B, Lindberg G, Lindblad U, Isacsson SO, Melander A, Rastam L. Incidence of myocardial infarction in elderly men being treated with antihypertensive drugs: population based cohort study. *BMJ*. 1996;313:457–461.
17. Bulpitt CJ, Beevers DG, Butler A, Coles EC, Hunt D, Munro-Faure AD, Newson RB, O'Riordan PW, Petrie JC, Rajagopalan B. The survival of treated hypertensive patients and their causes of death: a report from the DHSS Hypertensive Care Computing Project (DHCCP). *J Hypertens*. 1986;4:93–99.
18. Lindholm L, Ejlertsson G, Schersten B. High risk of cerebro-cardiovascular morbidity in well treated male hypertensives: a retrospective study of 40–59-year-old hypertensives in a Swedish primary care district. *Acta Med Scand*. 1984;216:251–259.
19. Isles CG, Walker LM, Beevers GD, Brown I, Cameron HL, Clarke J, Hawthorne V, Hole D, Lever AF, Robertson JW. Mortality in patients of the Glasgow Blood Pressure Clinic. *J Hypertens*. 1986;4:141–156.
20. Du X, Cruickshank K, McNamee R, Saraee M, Sourbutts J, Summers A, Roberts N, Walton E, Holmes S. Case-control study of stroke and the quality of hypertension control in north west England. *BMJ*. 1997;314:272–276.
21. Grobbee DE, Hoes AW. Confounding and indication for treatment in evaluation of drug treatment for hypertension. *BMJ*. 1997;315:1151–1154.
22. Verschuren WMM, van Leer EM, Blokstra A, Seidell JC, Smit HA, Bueno de Mesquita HB, de Oberman-Boer GL, Kromhout D. Cardiovascular disease risk factors in the Netherlands. *Neth J Cardiol*. 1993;6:205–210.
23. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol*. 1991;7:403–422.
24. Sjahid SI, van der Linden PD, Stricker BH. Agreement between the pharmacy medication history and patient interview for cardiovascular drugs: the Rotterdam elderly study. *Br J Clin Pharmacol*. 1998;45:591–595.
25. Klungel OH, de Boer A, Paes AHP, Herings RMC, Seidell JC, Bakker A. Agreement between self-reported antihypertensive drug use and pharmacy records in a population-based study in the Netherlands. *Pharm World Sci*. In press.
26. Cox DR. Regression models and lifetables. *J R Stat Soc (A)*. 1972;2:187–220.
27. Rothman KJ, Greenland S. *Modern Epidemiology*. Philadelphia, Pa: Lippincott-Raven; 1998.
28. Rijksinstituut voor Volksgezondheid en Milieu. Bijlage 5: Overzicht van epidemiologische kengetallen. In: Maas IA, Gijsen R, Lobbezoo IE, Poos MJJC, eds. *Volksgezondheid Toekomstverkenning 1997, I: De gezondheidstoestand: een actualisering*. Maarssen, Netherlands: Elsevier/De Tijdstroom; 1997:853–855.
29. Klungel OH, de Boer A, Paes AHP, Seidell JC, Bakker A. Influence of correction for within-person variability on the prevalence estimation of hypertension, treatment and undertreatment of hypertension. *Pharmacoepidemiol Drug Safety*. 1997;6:S25. Abstract.
30. Wingard DL. The sex differential in mortality rates: demographic and behavioral factors. *Am J Epidemiol*. 1982;115:205–216.
31. Wingard DL, Cohn BA, Kaplan GA, Cirillo PM, Cohen RD. Sex differentials in morbidity and mortality risks examined by age and cause in the same cohort. *Am J Epidemiol*. 1989;130:601–610.
32. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J*. 1986;111:383–390.
33. Bonneux L, Looman CWN, Barendregt JJ, van der Maas PJ. Regression analysis of recent changes in cardiovascular morbidity and mortality in the Netherlands. *BMJ*. 1997;314:789–792.